

## REMARKS

Claims 1, 3 through 7, 13, 14, and 16 are pending.

Reexamination and reconsideration of this application, withdrawal of all rejections, and formal notification of the allowability of the pending claims are earnestly solicited in light of the remarks which follow.

### *The Claimed Invention is Patentable in Light of the Art of Record*

Claims 1, 3 through 7, 13, 14, and 16 stand rejected over United States Patent No. 5,696,254 ("US 254") to Mansour et al. in view of United States Patent No. 6,051,709 ("US 709") to Goodyear et al.

It may be useful to briefly consider the invention before addressing the merits of the rejection.

Emtricitabine is a known antiviral drug. Emtricitabine is produced using a series of reactions, resulting in the introduction of both an oxathiolane moiety and a fluorocytosine moiety into the final compound. The introduction of a leaving group (LG) onto the oxathiolane moiety results in a racemic mixture. The emtricitabine isomer having the greatest therapeutic effect is the cis-enantiomer. Unfortunately, the separation of the emtricitabine cis-enantiomer from its isomeric mixture has heretofore been highly problematic.

Altogether unexpectedly in light of conventional wisdom, Applicants have found that a particular intermediate formed during the production of emtricitabine can readily be separated out as its salt, e.g. by reacting the intermediate (XIa) with an organic or inorganic acid to form a salt. This specific intermediate (XIa) includes the oxathiolane moiety, the fluorocytosine moiety,

and the menthol (chiral auxiliary) moiety. The ability to form an isolable salt is particularly surprising in light of the fact that the intermediate (XIa) in its free base form is an unfilterable gel. In that regard, the Examiner's attention is kindly directed to the Application-as-filed on Page 8, line 20 through Page 9, line 20.

Applicants respectfully submit that, in contrast to the separation of the specific recited intermediate, traditional methods of separation either occur much earlier within the reaction protocol, i.e. prior to fluorocytosine addition (US 254), or much later in the reaction protocol, i.e. on the end-product subsequent to the removal of the chiral auxiliary (US 709).

Thus the cited references do not teach or suggest the claimed invention.

US 254 is generally directed to the formation of an initial transoxathiolane compound (VII) to which an acetate leaving group (LG) is reacted, resulting in a racemic mixture of an oxathiolane/LG intermediate (IX).<sup>1</sup> Menthol, a chiral auxiliary, is reacted onto the oxathiolane/LG intermediate (IX) to form a racemic menthol/oxathiolane/LG intermediate (X) mixture. This racemic menthol/oxathiolane/LG intermediate (X) is separated into enantiomers by fractional crystallization. US 254 further notes that enzymatic resolution may be used in lieu of fractional crystallization. (Col. 9, lines 64 – 67). The LG of the resulting cis-menthol/oxathiolane/LG intermediate (X) is then replaced with fluorocytosine to form cis-menthol/oxathiolane/fluorocytosine intermediate (XI). The menthol group is subsequently removed from the cis- menthol/oxathiolane/fluorocytosine intermediate (XI) via a reduction

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<sup>1</sup> Applicants respectfully make of record that discrepancies have been observed relating to the stereochemistry of the intermediates used by US 254 to obtain emtricitabine, as noted in the Application-as-filed on Page 3, lines 16 through 17.

reaction to form emtricitabine (Ia). (Cols. 13 and 14, SCHEME 2 B)<sup>2</sup>. Example 21 of US 254 indicates that the resulting emtricitabine free base is subsequently purified using chromatography. (Col. 43, Ex. 21, lines 1 – 31).

Applicants respectfully submit that US 254, expressly teaching fractional crystallization, does not teach or suggest the inventive methods of forming salts that can be readily isolated from a solvent. US 254 instead expressly teaches enzymatic resolution as an alternative to fractional crystallization.

Nor does US 254, expressly teaching the fractional crystallization of a racemic intermediate containing a leaving group, teach or suggest the separation of a menthol/oxathiolane/fluorocytosine intermediate. Nor would there have been any motivation for US 254 to have done so, as US 254 had separated its intermediate compound by fractional crystallization well before the fluorocytosine reaction. Furthermore, US 254 would have had no expectation of success in such a separation, as menthol/oxathiolane/fluorocytosine free base forms an inseparable gel.

US 254 thus most certainly does not teach or suggest the recited salification of a menthol/oxathiolane/fluorocytosine intermediate. As noted above, there would there have been no motivation for US 254 to have done so and there further would have been no expectation of success.

Accordingly, Applicants respectfully submit that US 254 does not teach or suggest the claimed invention, considered either alone or in combination with the art of record.

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<sup>2</sup> Applicants respectfully make of record that the cited scheme 2A of US 254 refers to a different intermediate enantiomer. Applicants respectfully assume that Scheme 2B was instead intended, in conformance with the Application-as-filed on Page 1, lines 30 – 35.

US 709 does not cure the deficiencies in US 254.

US 709 is generally directed to a processes to form lamivudine, a non-fluorinated analogue of emtricitabine. (Col. 1, lines 15 – 30). US 709 initially reacts a mentholated oxathiolane chloride with a silylated purine or pyrimide base. (Col. 9, Scheme 1, line 30 – Col. 10, line 20 and Col. 6, lines 35 - 37). US 709 removes the menthol from the intermediate and subsequently reacts the de-mentholated compound with salicyclic acid in an aqueous solution. (Col. 11, lines 44 - 46). US 709 indicates that the “process of the invention” and prior processes produced lamivudine exhibiting a high solubility in water, making production difficult. (Col. 6, line 64 – Col. 7, line 3). US 709 goes on to note that one of its discoveries is a means by which to separate the end-product by adjusting its solubility. (Col. 7, lines 3 – 5). US 709 further notes that the salicylate may subsequently be converted to the free base by treatment with a base, such as triethylamine. (Col. 7, lines 5 – 7 and lines 45 – 47). The sole working example of US 709 is directed to lamivudine. (Col. 10, line 26 – Col. 12, line 5).

Applicants respectfully submit that US 709, expressly teaching the salification of the end-product lamivudine, does not teach or suggest the recited salification of a menthol/oxathiolane/fluorocytosine intermediate, as recited in the claimed invention. In fact, the impetus of US 709 is the formation of an insoluble end-product, and Applicants respectfully submit that the Office Action’s urgings at Page 5, second paragraph to the contrary are incorrect. Furthermore, Applicants respectfully submit that there would have been no expectation of success based on US 709. Applicants have found that the lamivudine of US 709 produces a filterable solid. In contrast, the claimed intermediate (XIa) forms a gel that is inseparable from the mother liquors by filtration, as noted in the Application-as-filed on Page 4, line 34 through Page 5, line 9. Hence there likewise was no reasonable expectation that the recited salification of the intermediate (XIa) would produce an isolable solid.

Accordingly US 709 does not teach or suggest the claimed invention, considered either alone or in combination with the remaining art of record.

Applicants respectfully submit that there would have been no motivation to have combined these references. However, even if Applicants had combined the foregoing references (which they did not) the claimed invention would not have resulted.

In particular, the combination of US 254 and US 709 would, at best, have resulted in the salification of the emtricitabine end-product. Accordingly, the combination does not teach or suggest the recited salification of a menthol/oxathiolane/fluorocytosine intermediate, as recited in the claimed invention. Specifically, US 709 expressly teaches the salification of the lamivudine end-product, not an “intermediate,” as urged within the outstanding Office Action on Page 3, fourth paragraph and Page 5, second paragraph. Applicants respectfully submit that the Office Action’s further assertions as to motivations for forming the salt of the menthol ester are merely conjecture based on a hindsight analysis and not the result of any optimization. Applicants respectfully reiterate that there would have been absolutely no expectation of success in forming the inventive isolable salt from the menthol/oxathiolane/fluorocytosine intermediate because its free base produces an inseparable gel.

Accordingly, Applicants respectfully submit that the claimed invention is patentable in light of US 254 and US 709, considered either alone or in combination.

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### CONCLUSION

It is respectfully submitted that Applicants have made a significant and important contribution to the art, which is neither disclosed nor suggested in the art. It is believed that all of pending Claims 1, 3 through 7 and 13, 14 and 16 are in condition for immediate allowance. It is requested that the Examiner telephone the undersigned if any questions remain to expedite examination of this application.

It is not believed that fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional fees are necessary to allow consideration of this paper, the fees are hereby authorized to be charged to Deposit Account No. 50-2193.

Respectfully submitted,

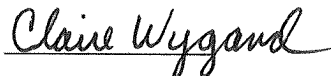


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Ms. Claire Wygand